UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

BTG INTERNATIONAL LIMITED, et al. Plaintiffs, v. AMNEAL PHARMACEUTICALS LLC, et al. Defendants.	Honorable Kevin McNulty, U.S.D.J. Civil Action No. 15-cv-5909 (KM) (JBC)
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, v. AMERIGEN PHARMACEUTICALS, INC., AND AMERIGEN PHARMACEUTICALS LTD., Defendants.	Honorable Kevin McNulty, U.S.D.J. Civil Action No. 16-cv-2449 (KM) (JBC)
BTG INTERNATIONAL LIMITED, et al., Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC., Defendant.	Honorable Kevin McNulty, U.S.D.J. Civil Action No. 17-cv-6435 (KM) (JBC)

DEFENDANTS' POST-TRIAL RESPONSE BRIEF

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INTRODUCTION

Janssen's post-trial brief confirms that it failed to prove infringement, and that the '438 patent is also invalid. The Court should enter judgment for Defendants.

No infringement. Janssen concedes that, to infringe, prednisone must have "anti-cancer effects" when used with abiraterone. PBr. 9.[1] But no one has tested that. Janssen's ongoing testing with prednisone has failed to replicate the 001 study results achieved with dexamethasone. *See* DTX 1712.2. And recent peer-reviewed articles confirm that prednisone's ability to fight cancer "as a single agent *or in combination* [including with abiraterone], remains unclear." DFOF 82-84. In the face of this contrary evidence, Janssen offers nothing. It thus failed to carry its burden.

Janssen's brief also confirms that it failed to prove the heightened requirements for its indirect infringement claims. An "'artificial' infringement claim … lies only against a patented use that has been *approved by* the FDA." *Bayer Schering Pharma AG v. Lupin Ltd.*, 676 F.3d 1316, 1319 (Fed. Cir. 2012) (citations omitted) (emphasis added). Janssen cannot satisfy this standard.

Janssen has no evidence that FDA approved the patented use. It never asked FDA, for the first time, to approve prednisone to fight cancer, never told FDA that prednisone fights cancer, and never submitted any data to FDA—much less the required "substantial evidence" from an "adequate and well-controlled study"—showing that prednisone fights cancer. *See* DFOF 189-192, 93-95, 141-155. As a result, FDA requires Janssen to tell the public that the role of prednisone is to help Zytiga work safely. DFOF 217-228. That is how Janssen markets Zytiga. DFOF 219-228. According to FDA-approved presentations, it is also what Dr. Rettig told doctors. DFOF 213-216. And it is what Janssen told patients in a recent study for Zytiga. DFOF 204-212. Defendants'

[1] Plaintiffs' and Defendants' proposed findings of fact and briefs are abbreviated as "PFOF," "DFOF," "PBr.," and "DBr." *See* ECF Nos. 549, 534, 535, 533.

generic versions of Zytiga are made solely for this *non-patented*, FDA-approved method—a method the Court held is "omit[ted]" from the claims. ECF No. 239 at 15; *see also* PFOF 708. This is a complete defense to Janssen's infringement claims. *See*, *e.g.*, *Bayer*, 676 F.3d at 1319, 1326.

Janssen also failed to prove that the accused labels *actively* induce—i.e., "encourage, recommend or promote"—infringement. *Takeda Pharms. U.S.A., Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) (citations omitted). The labels call for using abiraterone with prednisone, but not for "anti-cancer effects." PBr. 9. As Janssen's own cited authority makes clear, "[t]he question is not just whether [those] instructions describ[e] the infringing mode, ... but whether the instructions *teach an infringing use* such that we are willing to infer from those instructions an affirmative intent to infringe." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017) (citing *Takeda*, 785 F.3d at 631). There is no such teaching here.

Janssen has failed to prove infringement, and thus this Court need not address invalidity.

Invalidity. Trial also confirmed that the '438 patent is invalid. At the patent's priority date, a POSA would have been motivated to use prednisone with abiraterone to fight cancer, manage known abiraterone-induced side effects, and palliate pain. FDA even warned Janssen before the priority date that abiraterone's side effects would require adding a glucocorticoid. And in 2004, two years before the priority date, the critical O'Donnell publication reported on abiraterone's promise and warned that it may be necessary to use glucocorticoids. Thus, the prior art is clear.

As is Janssen's motivation. Its patent on abiraterone—the '213 patent—expired in 2016. To stave off generic competition, Janssen portrays abiraterone as a "dead drug" based on testimony from a newly added inventor and recasts prednisone as a cancer fighter. But whether the invention of the '438 patent is obvious must be viewed through the lens of the prior art. And through this lens, the patent is obvious—as the PTAB has found three times. This Court should do the same.

ARGUMENT

I. Janssen failed to meet its burden to show infringement.

The parties agree that Janssen must show not only that Defendants' products will cause direct infringement, but also that the accused product labels will induce or contribute to infringement. *See* PBr. 8-9. Janssen failed to meet its burdens at every step.

A. Janssen failed to prove direct infringement.

As for direct infringement, Janssen faces a major evidentiary problem: No one has ever tested whether prednisone is "therapeutically effective" to fight cancer in "a human" when used with abiraterone—much less proved all the elements of claim 1. JTX 8000 at cl. 1. Faced with, at best, "unclear" data to support direct infringement—as confirmed by recent literature and Janssen's own testing, DFOF 84—Janssen attempts to skirt the law and the evidence. The attempt fails.

1. Janssen failed to prove—as it must—that prednisone fights cancer when used with abiraterone.

To prove direct infringement, Janssen had to show that prednisone will be used in "an amount that has anti-cancer effects" when administered with Defendants' abiraterone products. PBr. 9. According to Janssen, dependent claims "specifically identif[y] the 'therapeutically effective amount' of prednisone to include 10 mg/day[.]" PBr. 10. That is not enough.

For one thing, the Court adopted Janssen's construction requiring that cancer be fought by *both* abiraterone *and* prednisone. Absent "proof" that both compounds fight cancer, the claims are not infringed. *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1310 (Fed. Cir. 2001). Neither the specification nor the dependent claims prove that 10 mg/day—or any amount—of prednisone fights cancer. To avoid this conclusion, Janssen points to a case involving a challenge to the definiteness of the patent claims at issue (*see* PBr. 10 (citing *King Pharm., Inc. v. Purdue Pharma., L.P.*, 718 F. Supp. 2d 703, 717-18 (W.D. Va. 2010)), but that is not the issue here. We know exactly

what the patent claims. What we lack is evidence that its claims are infringed.

Moreover, "dependent claims cannot be found infringed unless the claims from which they depend have been found to have been infringed." *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). Because Janssen failed to prove the "therapeutically effective amount of prednisone" element of claim 1, "the Court need not address the remaining dependent claims." *Supernus Pharm. Inc. v. Actavis Inc.*, 2016 WL 527838, at *28 (D.N.J. Feb. 5, 2016), *appeal dismissed* (May 10, 2016), *aff'd*, 665 F. App'x 901 (Fed. Cir. 2016).

It is no answer to say that proving direct infringement would require extensive testing; after all, there would be no direct infringement even if "it may be impossible to prove" what the patent claims. *Galderma Labs., L.P. v. Amneal Pharms., LLC*, 2018 WL 4179058, at *31 (D. Del. Aug. 29, 2018). Nor can Janssen pursue the circular argument that the claimed effects must occur because that is what the patent says. *See Research Found. v. Mylan Pharms. Inc.*, 809 F. Supp. 2d 296, 321-22 (D. Del. 2011) (finding no infringement even though accused product was a preferred embodiment of the patent), *aff'd in relevant part*, 531 F. App'x. 1008 (Fed. Cir. 2013).

Finally, Janssen may not protest that we "have offered no evidence demonstrating that prednisone, in combination with abiraterone, is *not* therapeutically effective." PBr. 16 Janssen argued for the governing construction and now "must supply sufficient evidence to prove that the accused product or process meets every element or limitation" by a preponderance of the evidence. *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997). It has failed to do so. While Janssen argues that "Defendants have offered no evidence demonstrating that prednisone, in combination with abiraterone, is not therapeutically effective," PBr. 16, Janssen cannot legally shift the burden to Defendants to prove a negative.

2. Janssen failed to prove what it now claims—namely, that prednisone fights cancer when used with abiraterone.

Janssen's brief is also notable for what it does *not* say. Janssen never argues that it designed a study to test whether prednisone fights cancer when used with abiraterone. The closest it has come is its ongoing study to show that abiraterone is safe and effective *without* prednisone. While this study incorporated a design "very similar" to that used in the 001 extension study (PFOF 585), it failed to replicate the 001 study results with prednisone. *See* DTX 1712.2. Left with no testing data to show direct infringement, Janssen overstates the 001 study results and tries to cobble together data from disparate studies. These efforts are unpersuasive, and certainly not enough to carry its burden.

First, Janssen relies on anecdotal evidence regarding dexamethasone. That is not enough, especially given that the 001 study results were never replicated with prednisone. DFOF 65, 69. And despite Dr. Rettig's characterizations, at most the results "suggest" that dexamethasone "may" reverse resistance to abiraterone. PFOF 154-56. But Janssen never proved this hypothesis. This explains why (1) Janssen never told FDA that the 001 study proved that *prednisone* fights cancer; (2) Janssen never tells the public that prednisone fights cancer; and (3) recent articles say that prednisone "was combined routinely with abiraterone [in Phase 3 studies] to mitigate mineralocorticoid excess"—not to fight cancer. DTX-1573.2 (citing JTX 8091, 8104). As Janssen's own employees conceded, no one could credibly claim that prednisone fights cancer without more proof. FOF 153.

To avoid these conclusions, Janssen overstates the 001 study results. Citing Attard 2009, Janssen says "the median time to PSA progression ("TTPP") for the 30 patients receiving the combination therapy [in 001] was approximately 150 days longer than the TTPP for patients on abiraterone alone." PBr. 11. But no witness testified to this data, and no article discussing the 001

data drew the unsupported conclusions that Janssen's attorneys now draw. And no wonder. The attorneys are comparing TTPP data from the "group 1" and "group 2" (abiraterone plus dexamethasone extension study) patients with the abiraterone monotherapy (main study) patient group in Attard 2009, even though the statistical confidence intervals heavily overlap. *See* JTX 8086.4-5 (showing confidence intervals of "55 to 688 days," "241 to 480 days," and "157 to 301 days," respectively). There is no basis to conclude from the 001 data that TTPP results were better for patients taking abiraterone-plus-dexamethasone than for those taking only abiraterone. *See* DFOF 80. Nor do any of the articles relied on by Janssen discuss "patients' scans, blood tests, and symptoms" to support Dr. de Bono's "reversal of resistance" hypothesis. The 001 study results thus fail to prove that prednisone actually fights cancer.

Tacitly acknowledging that it never tested prednisone, Janssen relies heavily on Dr. Rettig's comparison of the 001 and 002 studies and speculates that "FDA would have performed the same cross-study comparison." PFOF 624; PBr. 29-30. But there is no evidence that FDA looked into whether prednisone fights cancer or that Janssen asked it to do so. *See* DFOF 77, 181-192. And no one outside this litigation has relied on this analysis to suggest that prednisone might fight cancer. Dr. Rettig's contrived comparison reviews data with overlapping confidence intervals, ignores confounding differences, and overlooks conflicting data.[2] *See* DFOF 79-81. That is why the PTAB found Dr. Rettig's analysis unpersuasive (DTX 1562.35-36), and so too should this Court.

In sum, Janssen failed to make the threshold showing of direct infringement. By itself, that

[2] It is worth noting that Janssen misunderstands Dr. McKeague's testimony with respect to the last point. *See* PBr. at 20-21. Dr. McKeague acknowledged that up to 38% of patients in the 003 study received a steroid from the start of the study, but that "[would] not affect the median" time to PSA progression. Tr. 1036:19-24 (McKeague). He further testified that the Danila 2010 article, which was published in the *Journal of Clinical Oncology*, refers to the 003 study as measuring the "effects of abiraterone acetate (AA) monotherapy." JTX 8090.4; Tr. 1033:2-4 (McKeague).

warrants judgment for Defendants of non-infringement.

B. Janssen failed to prove induced infringement.

Janssen's post-trial brief confirms that it failed to prove inducement for two additional reasons. First, FDA has not approved the patented method. Second, Defendants' accused labels do not actively encourage, recommend, or promote infringement. Janssen has no credible answer.

1. Janssen failed to show that FDA approved the patented use.

a. Janssen again distorts the law: it must show that FDA approved the specific use claimed by the ′438 patent.

According to Janssen, whether FDA approved the patented use of both abiraterone and prednisone to fight cancer "is legally irrelevant." PBr. 25. But the Federal Circuit repeatedly has held that there can be no induced infringement where, as here, the "use claimed in the patent is not FDA-approved." *Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1332-34 (Fed. Cir. 2003); *see also Bayer*, 676 F.3d at 1319 ("[an] 'artificial' infringement claim … lies only against a patented use that has been approved by the FDA") (citations omitted); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364-65 (Fed. Cir. 2003) ("the request to make and sell a drug labeled with a permissible (noninfringing) use cannot reasonably be interpreted as an act of infringement (induced or otherwise) with respect to a patent on an unapproved use").

To avoid these precedents, Janssen suggests that FDA need not approve the *entire* patented use, only part of it. Janssen first concedes that "[t]he question for purposes of 271(e)(2) is … whether the use of abiraterone for which Defendants seek approval is both patented *and FDA approved*." PBr. 25-26 (emphasis added). But then Janssen says its can show infringement as long as FDA has approved *abiraterone*; and "the precise role the FDA understood *prednisone* to play" is irrelevant. *Id.* at 26. Not so.

Under Section 271(e)(2), there is no infringement unless the generic applicant "submit[s]"

its ANDA "for a drug … the use of which is claimed in a patent[.]" As this Court held, the "use" of abiraterone with prednisone to achieve "glucocorticoid replacement" is "omit[ted]" from the claims. ECF No. 239 at 15; *see also* PFOF 708. By statute, therefore, when Defendants ask FDA to approve using generic abiraterone with prednisone to replace glucocorticoids, they are not submitting ANDAs "for a drug … the use of which is claimed in a patent." 35 U.S.C. § 271(e)(2).

In the face of the statute's plain meaning, Janssen insists that an ANDA seeking approval for *any* use of abiraterone shows specific intent to market the product for the patented use. Not so. "The [Hatch-Waxman] statutory scheme … contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones." *Caraco Pharm. Labs. v. Novo Nordisk A/S*, 132 S. Ct. 1670, 1681-82 (2012). This remains true even if practicing the unapproved, patented use inevitably happens while practicing the FDA-approved, non-patented use. A "generic drug applicant c[an] not be liable for infringement … even [if the drug] necessarily ha[s] [the patented] effects in patients who t[ake] the drug for the approved purpose." *Bayer*, 676 F.3d at 1321 (citing *Allergan, Inc. v. Alcon Labs.*, 324 F.3d 1322, 1324 (Fed. Cir. 2003)). Indeed, "[b]ased on *Warner-Lambert* and *Allergan*, the defendants' conduct would constitute infringement … *only* if the defendants' ANDAs sought approval for the use protected by the … patent." *Id.* (emphasis added). That did not happen here.

It is no answer to observe that the patents in *Warner-Lambert*, *Allergan*, and *Bayer* "claimed uses different from the FDA-approved uses of the drugs that were the subject of the defendants' ANDAs." PBr. 26. The same is true here. Janssen itself highlighted the difference between (1) the patented use of abiraterone with prednisone to fight cancer, and (2) the non-patented use of abiraterone with prednisone to address side effects. PBr. 7; PFOF 708. As Janssen told this Court during claim construction, only the former use of abiraterone is patented—because the patent "must

be given a restrictive construction that encompasses *only* [the use of both abiraterone and prednisone for] 'reducing the growth and spread of cancer cells.'" ECF No. 239 at 3.

In short, Janssen's inducement claims are legally barred unless it shows that FDA approved using abiraterone with a "therapeutically effective amount of prednisone"—that is, enough prednisone to fight cancer in a human. Janssen came nowhere close to making that showing.

b. The record overwhelmingly showed that FDA never approved prednisone to fight cancer with abiraterone (or otherwise).

Backpedaling, Janssen says FDA somehow approved—without data or an application—a "therapeutically effective amount of prednisone" to fight cancer with abiraterone. Again, not so.

While the Zytiga indication is vague as to prednisone's role (see below), the administrative record is replete with statements by FDA confirming that prednisone's role is solely for safety:

- During 2005, FDA "explained that FDA's concern is mineralocorticoid excess and suggested Cougar use a glucocorticoid … such as prednisone" in abiraterone studies. DTX 1323.7; DFOF 167. FDA "reiterated that steroid supplement[s] should be given during any multiple dosing with abiraterone" and expressed "concern for mineralocorticoid excess with abiraterone." DTX 1326.6; DFOF 166.

- In 2011, FDA reviewers found that "[a]biraterone acetate is given concurrently with 10 mg of prednisone once daily in order to attenuate mineralocorticoid excess resulting from reduced feedback inhibition of ACTH." DTX 1333.107; DFOF 198.

- In 2011, FDA also found that "[t]he efficacy and safety findings from the clinical review of this NDA provide substantial evidence for the effectiveness of *abiraterone acetate*"—without mentioning prednisone's efficacy. DTX 1336.5 (emphasis added); DFOF 195.

- In 2012, FDA explained that "[p]rednisone has been given with abiraterone to suppress ACTH and to provided needed glucocorticoids." DTX 1340.53; DFOF 200.

FDA was right. Janssen itself required using prednisone to improve safety after a patient on abiraterone alone died. As explained at trial, in a March 2008 letter, Janssen (Cougar) notified clinical investigators about the death and said in no uncertain terms: "Patients receiving abiraterone acetate monotherapy … must *now* begin prednisone." DTX 1354.4 (emphasis added); *see also*

DFOF 169-174. In its brief and proposed findings of fact, Janssen ignores this key letter.

Despite this overwhelming record, Janssen insists that "the administrative record made clear to FDA that prednisone contributes to the efficacy of the combination." PBr. 32. In reality, neither Janssen nor FDA mentioned prednisone fighting cancer, much less concluded that prednisone should be taken with Zytiga for that purpose. Of course, FDA had the 001 study data, but Janssen never explained how data for dexamethasone could support anti-cancer efficacy for prednisone. Nor was FDA given any of the literature that discusses the 001 data or Dr. de Bono's hypothesis until after Zytiga's first approval, and there is no evidence that FDA ever relied on those articles for later approvals. DFOF 122; *compare* PFOF 617-618 (incorrectly implying otherwise); *see also* Tr. 908:17-23. Prednisone was always used for safety—period.

Thus, it is fanciful to suggest that FDA nonetheless approved the patented method. Again, Janssen never asked FDA to approve prednisone to fight cancer or submitted data to show that it did. DFOF 175-192. Instead, when applying for Zytiga's approval in December 2010, years after filing the '438 patent and after the 001 study was completed, Janssen told FDA that abiraterone should be used with prednisone for a non-patented method: "Concurrent treatment with prednisone (5 mg twice daily) is administered to ameliorate mineralocorticoid-related toxicity that was observed with abiraterone acetate in early Phase 1/2 studies." JTX 8187.54; DFOF 187. Janssen never mentioned a "reversal of resistance theory" to FDA, or otherwise suggested that prednisone fights cancer.

Not surprisingly, FDA has not allowed Janssen to market Zytiga for the patented method. Instead, Janssen's FDA-approved marketing materials inform doctors (through Dr. Rettig, among others on Janssen's speakers' bureau), patients (through the LATITUDE informed-consent form) and the public (through the Zytiga website and marketing materials) that prednisone is for safety:

- A "Key Point" from Dr. Rettig's FDA-approved physician slide presentation for Janssen was that "co-administration of a corticosteroid suppresses adrenocorticotropic hormone drive, resulting in a reduction in the incidence and severity of the adverse reactions of hypokalemia, hypertension, and fluid retention." DTX 1697.66; DFOF 214-215; *see also* Tr. 673:16-674:17 (document used to impeach Dr. Rettig).

- Janssen's "Putting Prednisone in Perspective" brochure devoted to "[u]nderstanding the role of prednisone in combination with ZYTIGA®" says the indication requires using prednisone to "reduce[] the incidence and severity of mineralocorticoid-related adverse reactions associated with ZYTIGA® (abiraterone acetate)." DTX 1274.4; DFOF 219-220.

- Janssen's marketing document entitled "Now Examine the Effect of Zytiga" similarly states that "[p]rednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions with Zytiga®." DTX 1260.1; DFOF 221.

- The Zytiga website noted that "[b]ecause of the way Zytiga® works, certain side effects may occur." DTX 1235.3-4. It adds: "**Prednisone may help decrease the occurrence and severity of these side effects**." DTX 1235.3-4 (emphasis in original); DFOF 222.

- In the 2012 LATITUDE Informed Consent Form, Janssen told patients that "[a]lthough prednisone is commonly prescribed to patients with prostate cancer, it has not been approved to treat this disease." DTX 1585.2 (emphasis added); FOF 208. Instead, using prednisone "can reduce or eliminate some side effects" caused by abiraterone. DTX 1585.2, 13; DFOF 208, 210.

In response to all this, Janssen points to a few advertisements that describe results from the Phase III studies not designed to show that prednisone fights cancer because prednisone was in both study arms. PBr. 60 n. 33; *see also* DFOF 149. Janssen also says it "is permitted to discuss [the] safety benefits of prednisone in its advertising materials so long as they are truthful and supported by substantial evidence." PFOF 635. This misses the point. Janssen cites no evidence that it has ever said that prednisone's role is to fight cancer. Why? As Dr. Mega explained, if that were really prednisone's primary purpose, as Janssen argues, doctors and patients should have been told. DFOF 237. The truth is, Janssen never says prednisone fights cancer because that theory has never been supported by any data, much less approved by FDA, and doing so could violate off-label marketing rules—and perhaps even constitute a crime. DFOF 217. Janssen cannot show infringement.

2. Janssen failed to prove that the accused product labels actively induce infringement.

Janssen's inducement claims fail for an independent reason: the accused labels do not actively induce infringement.

a. Once again, Janssen distorts the law: inevitable infringement is not enough to show inducement.

According to Janssen, the accused product "labels clearly induce infringement because" they instruct "administering the same drugs in the same dosages to treat the same disease claimed in the '438 patent." PBr. 24. But again, the claims also require that *both* abiraterone *and* prednisone fight cancer. Brushing this aside, Janssen contends it merely needs to show that "the product labeling that Defendants seek would inevitably lead [all] physicians to infringe." PBr. 24 (citing *Eli Lilly*, 845 F.3d at 1369). That is incorrect. Labels do not *actively* induce infringement unless they teach and encourage all claim elements—which here includes using prednisone to fight cancer.

In short, there can be no active inducement unless the labels "encourage, recommend or promote" using both abiraterone and prednisone to fight cancer. *Takeda*, 785 F.3d at 631. In *Bayer*, for example, the label said that using the drug could cause the patented effects. Yet still there was no inducement because the label did "not do so in any way that recommends or suggests to physicians that the drug is safe and effective for administration to patients *for the purpose of inducing those effects*." 676 F.3d at 1322 (emphasis added). As Janssen's own case confirms, "[t]he question is not just whether [the label's] instructions describ[e] the infringing mode ... but whether the instructions teach an infringing use such that we are willing to infer from those instructions an affirmative intent to infringe the patent." *Eli Lilly & Co. v. Teva Parenteral Medicines, Inc.*, 845 F.3d 1357, 1368 (Fed. Cir. 2017) (citing *Takeda*, 785 F.3d at 631) (alterations in original).

Courts in this District faithfully apply these principles, holding that even if "a user following

the instructions may end up practicing the patented method," that "is not enough" to prove induced infringement. *In re Depomed Patent Litig.*, 2016 WL 7163647, at *58 (D.N.J. Sep. 30, 2016) (Cecchi, J.) (quoting *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, at *55 (D.N.J. Aug. 29, 2014)). In fact, even if the accused labels expressly permitted using abiraterone and prednisone in a way that directly infringed (they do not), "permission is different from encouragement." *In re Shire*, 2014 WL 2861430, at *5 (D.N.J. Jun 23, 2014). The labels here do not approach these high standards.

b. Janssen failed to show that the accused labels teach the patented method.

In fact, Janssen failed to prove that the accused labels "teach" the patented use of *both* abiraterone and prednisone to fight cancer. *Eli Lilly*, 845 F.3d at 1368. The Zytiga indication is vague at best as to prednisone's role. DFOF 115. While the indication instructs using Zytiga "in combination with prednisone for the treatment of patients with … prostate cancer," FDA used this precise phrasing in the indications for cancer drugs Taxotere and Jevtana. Yet both sides agree that prednisone is *not* used with either of those drugs to fight cancer. DFOF 46, 116-117. Janssen never adopts the unsupported testimony of its FDA expert, Ms. O'Shea, that FDA approved prednisone to fight cancer in the Taxotere and Jevtana labels. That testimony was not credible in view of contrary testimony from physicians on both sides. DFOF 45-46. Moreover, the Taxotere label is prior art: thus, Ms. O'Shea's testimony is inconsistent with Janssen's validity positions. *See* PBr. 42.

Simply put, nothing in the labels here teaches using prednisone to fight cancer. Rather, the original Zytiga label teaches using prednisone for safety: "Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions." PFOF 594-95. While FDA removed this statement from

the current label, it did not explain the deletion, and Janssen has not suggested that the role of prednisone has changed. DFOF 129. The warnings and precautions section still implies that prednisone should be used to address endocrine issues—that is, for safety. DFOF 126-135. And that is precisely how Janssen describes that role in its marketing materials. DFOF 215, 217-228.

Importantly, it is not Defendants' burden to point to something in the label explaining prednisone's role. Instead, Janssen "needs to show that [Defendants] took affirmative steps to induce, not affirmative steps to make sure others avoid infringement." *Takeda*, 785 F.3d at 632 n.4. Because Janssen cannot point to any portion of the Defendants' labels that shows affirmative steps to induce, it is left to rely on Dr. Rettig's testimony that physicians would need to consider documents *outside* the label, such as the Attard papers, to determine prednisone's role. *See* PBr. 29-30; DFOF 121. But courts have consistently rejected this type of "scavenger hunt theory." *See United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153, at *19 (D.N.J. Aug. 29, 2014); *see also* DBr. 30.

The law is clear: "vague label language cannot be combined with speculation about how physicians may act to find inducement." *Takeda*, 785 F.3d at 6332. As in *Bayer*, "the label neither provides a statement to th[e] effect [that following the label will cause the patented effects] nor summarizes any supporting research." 676 F.3d at 1325. Nor do those labels summarize any research supporting Janssen's contention that *both* drugs independently fight cancer—because there is none. This, too, defeats Janssen's inducement claims.[3] *See Acorda Therapeutics Inc. v. Apotex*

[3] Janssen asserts that Defendants' knowledge of alleged inducement is "undisputed" (PBr. at 9, PFOF 77-80), but this just shows Defendants knew the '438 patent was Orange Book-listed. Janssen did not introduce any evidence from Defendants to support our knowledge required for induced infringement, *i.e.*, knowledge that prednisone fights cancer when used with abiraterone. Defendants, in fact, do not have the requisite knowledge, because recent publications announce that prednisone does not actually treat cancer. DFOF 82-84.

Inc., 2011 WL 4074116, at *18 (D.N.J. Sept. 6, 2011) ("[a] label devoid of any information directly explaining" the patented method "cannot be said to encourage infringement[.]").

C. Janssen failed to prove contributory infringement.

For similar reasons, Janssen fails to show contributory infringement. First, there is no contributory infringement as a matter of law unless Janssen proves there will be direct infringement—which, as discussed, it failed to do. *Forest Labs., Inc.*, 239 F.3d at 1310. Second, as discussed, Defendants' ANDA products are not "especially made" for the patented use. 35 U.S.C. § 271(c). Rather, FDA approved using abiraterone with prednisone solely for safety.

Finally, Defendants' products are "suitable for substantial noninfringing use" (*id.*)—e.g., the non-patented, FDA-approved method of using abiraterone with prednisone for safety. Also, Janssen does not, because it cannot, argue that prednisone always contributes to fighting cancer. Even crediting the 001 study data, only one-third of the patients arguably obtained a "reversal of resistance" effect from dexamethasone. PFOF 133. That is, even under Janssen's own (flawed) theory that this proves that prednisone fights cancer, a substantial majority of patients following the accused labels will *not* directly infringe. This is a far greater percentage than the "less than 5%" of patients previously found to constitute a substantial noninfringing use. *In re Depomed Patent Litig.*, 2016 WL 7163647, at *67 (D.N.J. Sept. 30, 2016).

II. Defendants proved the '438 patent invalid by clear and convincing evidence.

In considering whether the claims of the '438 patent would have been obvious, "[t]he question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007). The inquiry is based on the prior art and what skilled artisans would have understood from that art at the priority date. It is not guided by an inventor's subjective, and often self-interested, retelling of his path to the alleged invention. Here, the prior art points a POSA to the

combination of abiraterone and prednisone. It does so in express and unequivocal language and in multiple highly reputed peer-reviewed journals.

Janssen attempts to recast the art, repeatedly suggesting that the purported invention was "contrary to popular wisdom" and clarified a field brimming with "confusion." In doing so, Janssen relies heavily on the testimony of one of the patent's three inventors, Dr. de Bono, a scientist Janssen added as an inventor to the '438 patent after this case began. DFOF 22, 295-304; PFOF 10, 50-52. But Dr. de Bono cannot now reinterpret the prior art, which Defendants showed unambiguously pointed to the claimed combination.

A. Janssen's "teaching away" arguments ignore the relevant legal standard.

Janssen argues that the prior art "taught away" from pursuing abiraterone, in any capacity, to treat prostate cancer, and also that the prior art taught away from combining abiraterone with prednisone. PBr. 38, 46, 51, 57-58. But the question here is whether it was obvious to use the claimed combination (abiraterone with prednisone), not whether it was obvious to use abiraterone alone. Janssen cannot credibly dispute that the latter was well known. As such, any evidence relevant to an alleged teaching away must address using prednisone with abiraterone. There is none.

And even as to abiraterone alone, "[a] reference does not teach away … if it … does not criticize, discredit or otherwise discourage investigation into the invention claimed." *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (alterations in original) (internal quotations omitted) (quoting *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009)). Yet Janssen says only that the prior art deemed second-line hormonal therapies "unexciting," and that other therapies "were considered more promising." PBr. 38. But "[a] teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions." *Galderma*, 737 F.3d at 739; *see also*

In re Mouttet, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("This court has further explained that just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes."). At best, Janssen has presented some evidence of disagreement about the promise of a class of drugs that includes abiraterone. That does not amount to teaching away.

Moreover, Janssen's alleged evidence that the art taught away from using abiraterone independently fails because it ignores contemporaneous art in favor of much older art. For example, Janssen ignores publications from O'Donnell in 2004 (DTX 1129.8), Attard in 2005 (JTX 8072.5) and Garnick in 2006 (DTX 1157.8), which were all published far closer to the 2006 priority date than Janssen's Lara reference from seven years earlier (which does not even mention abiraterone). PTX 39. All of these later references expressly touted abiraterone's promise in treating prostate cancer, such as by noting that abiraterone was "currently under development as a second-line hormonal therapy for prostate cancer." DTX 1157.8; *see also Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (finding that references closer to the priority date better inform the teaching away inquiry).[4]

Further, Janssen mistakenly insists that the prior art taught away from combining abiraterone and prednisone because of prednisone's purported toxic side effects. PBr. 46, 52, 57; PFOF 939-950, 970-983. Janssen ignores express teachings that prednisone's possible side effects occur only at higher doses. DFOF 491-500. By contrast, replacement doses of prednisone, including 10 mg, were *not* expected to cause significant side effects. *Id*. That exact dose of prednisone was approved by FDA in 2004 in combination with Taxotere for patients with prostate cancer. DFOF 102-103, 117. Faced with these teachings, Janssen points to a 1986 article reporting

[4] Janssen asserts that Garnick 2006 "did not suggest to a skilled person that abiraterone acetate should be selected as a starting point" (PFOF 775)—overlooking the next page, which states that abiraterone was *already selected* for development. DTX 1157.8.

that it "is not possible to stipulate a daily dose at which the risk of side effects is *non-existent*." JTX 8025.2 (emphasis added); Tr. 1960:11-1961:6. But a POSA would have expected that few drugs are entirely free of side effects, and it was still known that replacement doses of prednisone were safe. *See Galderma*, 737 F.3d at 739 (no teaching away where prior art did not "indicate in any way that the side effects would be serious enough to dissuade the development of" the claimed pharmaceutical); JTX 8025.2 ("In general, the lower the maintenance dose of a corticosteroid agent, the less risk of side-effects"; "it is likely that daily doses *in excess* of 10 mg of prednisone will eventually lead to some side effects.") (emphasis added).

Thus, Janssen failed to show that the prior art taught away from the use of abiraterone, alone or with prednisone, to treat prostate cancer.

B. Abiraterone held promise as a prostate cancer treatment, and it would have been obvious to use abiraterone with prednisone

Janssen also applies an incorrect legal standard to argue that a POSA would not have been motivated to combine abiraterone with prednisone, urging the Court to require definitive proof. But Defendants need only "identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. "[O]nly a reasonable expectation of success, not a guarantee, is needed." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). The evidence at trial satisfied this standard: At the 2006 priority date, a POSA viewed abiraterone as a promising prostate cancer treatment and had at least three different "reason[s] to combine" abiraterone and prednisone. *KSR*, 550 U.S. at 418.

Seeking to elevate Defendants' burden of proof, Janssen urges that a POSA would not have been motivated to combine abiraterone and prednisone because the combination was not guaranteed

to be effective, certain clinical benefits (such as survival) were not "proven,"[5] or the art did not "determine" whether the combination should be made. PBr. 42, 43, 48.[6] All these arguments lack merit.

1. The prior art identified abiraterone as a promising prostate cancer treatment.

Abiraterone was disclosed and described in multiple prior art references—including the '213 patent, the O'Donnell reference, and Attard 2005—as useful for treating androgen-dependent disorders like prostate cancer. JTX 8042.3; DTX 1129; DFOF 295-96, 577. In fact, these references, along with other older references from the 1990s, detailed abiraterone's specific cancer fighting mechanism. As of 2006, abiraterone was understood to be a potent and selective CYP17 inhibitor, and known to make men produce less testosterone. It was likewise understood that testosterone was the androgen that fueled prostate cancer. DFOF 262-63, 267, 295-301, 310-313.

Indeed, scientists at the Institute for Cancer Research successfully tested abiraterone in human trials, including the O'Donnell trials, several years before the priority date of the '438 patent to confirm that it would suppress testosterone synthesis. DFOF 302-306. The results from these trials were reported in the 2004 O'Donnell publication, which disclosed abiraterone's ability to suppress testosterone in patients with advanced prostate cancer. DFOF 311; DTX 1129.1 (text and Abstract). These results would have been recognized by and instructive to a POSA. *Id.*[7]

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[5] It is irrelevant whether treatments like glucocorticoids, ketoconazole, and other treatments achieve a survival benefit as of the priority date (*e.g.*, PFOF 754, 757, 763). A treatment in development in 2006 could have shown promise and then later achieved the ultimate survival benefit shown in phase III trials. *See*, *e.g.*, DBr. at 49-50. Indeed, abiraterone did not show a survival benefit until 2011. JTX 8091. Also, cancer treatments such as ketoconazole were routinely used despite never showing this benefit. DFOF 268, 274-275, 384; Tr. 2015:4-9 (Rettig).

[6] Janssen also improperly seeks to introduce evidence of private interactions (such as licensing), abiraterone's development, and publication failures into the *prima facie* obviousness case. PBr. at 34-35, 39-41, 50; PFOF 777-790.

[7] It is irrelevant that Dr. Lipton had not personally read O'Donnell before this case (PFOF 793-

According to Janssen, O'Donnell did not demonstrate that abiraterone was "effective." *See* PFOF 764-796. But O'Donnell demonstrated that abiraterone worked exactly as a POSA would have expected a CYP17 inhibitor to work, and its results would have motivated a POSA to further pursue abiraterone as a prostate cancer drug. DBr. 36. The evidence at trial demonstrated that a POSA would have known that abiraterone was developed as "a more selective inhibitor of the [CYP17] enzyme,"[8] making abiraterone a next-generation active prostate cancer agent. A POSA would have also understood that abiraterone was an improvement over drugs such as ketoconazole, to which O'Donnell repeatedly refers for context. DFOF 307-316; DTX 1129.2 (text and Fig. 1).[9]

Janssen argues that abiraterone would not have been considered a *leading* candidate for a prostate cancer therapy in 2006. But the question is "whether the prior art would have *suggested* to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process." *PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014) (emphasis added) (citations omitted). Defendants have met this standard. O'Donnell plainly established abiraterone's ability to reduce testosterone levels in humans, a key target in treating prostate cancer, and other publications further discussed abiraterone's promise. DFOF 308-16;

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794); obviousness is judged from the viewpoint of a POSA, who is presumed to know all relevant prior art. *See In re Carlson*, 983 F.2d 1032, 1037-38 (Fed. Cir. 1992).

[8] Janssen is mistaken that a POSA would not have pursued abiraterone because there were other "more potent" CYP17 inhibitors (PFOF 797-800), as a POSA would know that abiraterone was the most potent *and selective* CYP17 inhibitor in clinical studies at the priority date. DFOF 453, 455; JTX 8072.3-4 (reporting, in 2005, that "[t]he most potent and selective inhibitor of CYP450c17 [i.e., CYP17] currently in clinical studies is abiraterone acetate" and "[t]wo compounds, CB7598 (abiraterone) … and CB7627, were identified as the most potent, and were selected for further development … Unlike CB7627, abiraterone was a highly selective inhibitor of CYP450c17 and so was chosen as the main candidate for further development.").

[9] Although Janssen misunderstands Defendants' expert's testimony as to inferior drugs as referring to abiraterone (*see*, *e.g.*, PFOF 755), a POSA would have been aware that abiraterone was an exciting, next-generation steroid synthesis inhibitor. DBr. at 35-36.

DTX 1129.8 ("These studies demonstrate for the first time the potential utility of specific inhibition of 17α-hydroxylase/$C_{17,20}$-lyase in causing reductions in testosterone levels in both castrate and noncastrate males with prostate cancer."; "The present data … support the potential utility of [abiraterone] in the second-line treatment of [prostate cancer] patients who have become refractory to gonadotrophin-releasing hormone agonists."); JTX 8072.5; DTX 1157.8.

Janssen further argues that prostate cancer researchers were confused and uncertain—at least according to expert-type testimony from its fact witness, Dr. de Bono (*see* Section III, *infra*))—and that a POSA would have pursued other drugs. These arguments do not save the '438 patent. None of the prior art "taught away" from using abiraterone to treat prostate cancer. No reference questioned abiraterone's ability as a CYP17 inhibitor to reduce testosterone, nor did any reference criticize using prednisone with abiraterone.

Finally, Janssen points to a handful of irrelevant cases. For example, in *ViiV*, the drug at issue (carbovir) was one nondescript item in a "laundry list of drug classes and compounds" to be used in a combination of a 3-drug cocktail to treat HIV, giving a POSA "virtually no guidance as to which path to choose." *ViiV Healthcare UK Ltd. v. Lupin Ltd.*, 6 F. Supp. 3d 461, 493-94 (D. Del. 2013), *aff'd*, 594 F. App'x 686 (Fed. Cir. 2015). Here, in contrast, a POSA naturally would have looked to O'Donnell and its encouraging disclosures regarding abiraterone. O'Donnell provided clear experimental support from human studies, was published just two years before the priority date, and concluded that abiraterone was a next-generation testosterone-synthesis inhibitor that could provide a beneficial prostate cancer treatment. DTX 1129.1, 6-8.

2. A POSA would have been motivated to combine abiraterone and prednisone

The trial evidence showed that there were three separate motivations in the prior art to use prednisone with abiraterone: (1) as a second active cancer-fighter; (2) to address abiraterone's side

effects; and (3) to palliate cancer symptoms. Any *one* of these renders the '438 patent obvious.

a. A POSA would have been motivated to use prednisone as a possible second active agent with abiraterone

Unlike today, prednisone was believed to have a potential anti-cancer benefit as of 2006. The trial evidence showed that a POSA in 2006 would have been motivated to use prednisone with abiraterone to fight cancer. In particular, the prior art suggested that prednisone may have anti-cancer effects in prostate cancer patients, and a POSA would therefore have been motivated to combine abiraterone with prednisone to treat those patients.

The trial testimony established that Sartor was a 1998 peer-reviewed article, published in the journal Urology, that studied the effect of prednisone alone on PSA levels in prostate cancer patients. DFOF 460-65; DTX 1087.1. PSA levels can be a preliminary sign of a drug's potential to fight cancer. DFOF 462-65, 470. Sartor taught that treating patients with prednisone (20 mg per day, in two equally-divided doses) successfully reduced PSA levels in a significant number of those patients, and that a significant proportion of patients (1/7) responded for over six months. DFOF 466-73. A POSA reasonably would have read Sartor as supporting the conclusion that prednisone is well-tolerated and reasonably likely to reduce PSA levels in prostate cancer patients, suggesting that prednisone might be an effective treatment option. DFOF 474, 487-88.

Janssen's attacks on Sartor miss the mark. Janssen argues, for example, that by 2006 prednisone had not been "shown to provide a survival benefit," and that Defendants therefore "resort to arguing that the prior art was nonetheless 'suggestive'" of prednisone's anti-cancer effect. PBr. 42; *see also* PFOF 803-838 (also focusing on what practitioners know now about prednisone, not what the POSA would have expected in 2006). This misses the point. It is undisputed that the '438 patent claims do not require a survival benefit. Defendants need only show that the prior art "suggested" to a POSA to use prednisone to treat cancer. *PAR Pharm.*, 773 F.3d at 1196; *see also*

Mouttet, 686 F.3d at 1333 ("[T]he test for obviousness is what the combined teachings of the references would have *suggested* to those having ordinary skill in the art.") (emphasis added). By showing an effect on PSA levels, Sartor suggested to a POSA to use prednisone to fight cancer. This is all the law requires. Thus, it is no answer to say that Sartor did not "show[] a survival benefit" or "a durable response," or that the role of glucocorticoids "is not agreed upon by all." *Id*.

Janssen goes on to suggest that this Court should reexamine Sartor's findings, but none of Janssen's reasoning is persuasive. PBr. 43. *First*, Janssen's characterization of Sartor is questionable: Sartor never said in his later 2006 article that secondary hormonal agents had no survival advantage. Instead, the article noted that no study had *yet* demonstrated the advantage. PTX 108 at 238. There is a significant difference, because a POSA in 2006 would still have been encouraged by Sartor 1998's results and hoped prednisone would eventually achieve a survival benefit. DBr. at 46-47, 49-50. In fact, Sartor went on to ask, rhetorically, whether a POSA could improve prostate cancer treatment by combining two active agents for use in patients, and then noted that one combination therapy could include prednisone. PTX 108 at 238.

Second, Janssen says the testimony of Defendants' non-infringement expert Dr. Mega is inconsistent with a POSA's understanding that prednisone could have anti-cancer effects. PFOF 818, 836-838. But Dr. Mega simply and rightly testified that Sartor did not prove that prednisone treats prostate cancer, and that he did not know of any proof.[10] Here again, Janssen is applying the wrong test for obviousness. Under the correct test, the '438 patent's claims would have been obvious because the prior art *suggested* prednisone's use as an anti-cancer agent, not because the prior art *proved* it.

[10] Dr. Mega's testimony about what happened in 2006 also falls short because he did not opine on the obviousness of the '438 patent, judged from the viewpoint of a POSA aware of all relevant prior art in 2006. Tr. 1143:25-1144:4 (Mega).

Janssen's criticisms of Vidal are equally unavailing. Vidal is a 2004 article authored by Dr. de Bono himself. It discloses that testosterone can be produced in the adrenal glands of prostate cancer patients and proposes addressing this problem by administering steroids like prednisone and CYP17 inhibitors like abiraterone. DTX 1135.2-3. Vidal further concluded that "combinations" of therapies are "likely to be key in the future treatment of cancer." DTX 1135.6.

In response, Janssen is left to argue that when Vidal was published, the biological theory that led to the claims of the '438 patent was unknown and Vidal therefore could not have motivated a POSA to combine prednisone and abiraterone. PBr. 45; PFOF 839-858. Not so. Vidal explained that circulating low levels of steroids can cause a patient to fail to respond to hormone therapy. DTX 1135.2; DTX 1135.3 (citing O'Donnell); DFOF 484. Vidal expressly noted that "androgen-independent" prostate cancer could result from low levels of steroids binding to "hypersensitive [androgen receptor] complexes," despite "castrate" levels of testosterone, which is the exact mechanism that Dr. de Bono claimed is novel. DTX 1135.3.[11] Janssen's remaining theory, that Vidal and Sartor "teach away" from the use of prednisone, fails because none of the cited statements "criticize, discredit or otherwise discourage investigation *into the invention claimed*." *Galderma*, 737 F.3d at 739 (emphasis added) (internal quotations omitted) (citations omitted).

b. A POSA would have been motivated to use prednisone to manage abiraterone's side effects

Janssen disputes that a POSA would have turned to prednisone to manage abiraterone's known side effects, but that overlooks a POSA's knowledge in 2006. For example, Janssen argues that a POSA would not have expected abiraterone to cause adrenal insufficiency because

[11] This also rebuts Janssen's argument that simple use of terms like "androgen independent" and "hormone refractory" demonstrate confusion—Dr. de Bono, in Vidal, still used the term "androgen-independent" to describe how "androgen independent" prostate cancer would be treated by further reducing testosterone. PBr. 37-38; *see also* DBr. 56.

corticosterone could adequately compensate for abiraterone patients' reduced cortisol. PBr. at 47-48; PFOF 905, 916, 932. In reality, the prior art predicted adrenal insufficiency. DTX 1129.1, 7, JTX 8072.5. In fact, even in 2007—after the priority date—Janssen's endocrinologist recognized that "[t]he objective of adding glucocorticoid to abiraterone is to avoid real or *perceived* adrenal insufficiency." DTX 1450.2 (emphasis added). Perhaps today—due to results from Janssen's post-priority abiraterone studies—Janssen is aware that corticosterone can be produced in levels high enough to compensate for abiraterone patients' low cortisol, and prednisone addresses the resulting mineralocorticoid excess. *See*, *e.g.*, DTX 1274.2. But the obviousness standard hinges on what a POSA—correctly or incorrectly—perceived *in 2006*. *See*, *e.g.*, *In re Mayne*, 104 F.3d 1339, 1341 (Fed. Cir. 1997); *Novartis Pharms. Corp. v. Teva Pharms. USA, Inc.*, No. 05-cv-1887 (DMC), 2009 WL 3754170, at *12-13 (D.N.J. Nov. 5, 2009) (granting defendant's motion to exclude later-discovered toxicity evidence plaintiff sought to use to support its non-obviousness case). And a POSA in 2006 would have either expected adrenal insufficiency or mineralocorticoid excess, potentially being unsure which levels would rise or drop. A POSA would have understood, however, that prednisone would restore the balance, thus addressing either side effect. DBr. 37-42.

A POSA would have also anticipated these effects because the prior art disclosed abiraterone's impact on cortisol. DBr. at 37, 39-42. Janssen asserts that O'Donnell did not explicitly disclose mineralocorticoid excess in its 1- and 12-day studies. PFOF 918-927; *see also* PFOF 928-938. But O'Donnell did report abiraterone's "predictable" impact on cortisol, based on the steroid synthesis pathway. DTX 1129.7. Attard 2005, reviewing O'Donnell's data, anticipated that maybe adrenal insufficiency would occur—but if not, mineralocorticoid excess would occur. JTX 8072.3, 5; DBr. at 39-41. This is not "*Defendants'* either-or understanding of abiraterone's possible side effects." PBr at 51 (emphasis added)). It is what the prior art disclosed and

demonstrates what the POSA would have understood in 2006. JTX 8072.3, 5. Janssen notes that Attard 2005 "was a review article that contained no original data on abiraterone." PBr. at 51; PFOF 930. And indeed, Attard 2005 discusses O'Donnell's data and predicts mineralocorticoid excess—which is why Attard 2005 is so helpful to assess the POSA's understanding of O'Donnell. In short, the evidence shows Janssen is mistaken about the alleged complexity and confusion surrounding the steroid biosynthesis pathway. PFOF 860-867. O'Donnell, Attard, and others had no problem predicting abiraterone's likely side effects.

Janssen also argues that a POSA would not look to prednisone to address mineralocorticoid excess. PBr. at 53-54; PFOF 947-948. But again, a POSA would have predicted that either adrenal insufficiency or mineralocorticoid excess would occur because of abiraterone's predicted effect on cortisol levels. Prednisone was known to treat either condition. DBr. at 41-42. In fact, an FDA endocrinologist specifically recommended prednisone to address mineralocorticoid excess in 2005. DBr. at 41.

A POSA would have been further motivated to combine abiraterone with prednisone because prednisone was known to reduce side effects when administered with ketoconazole, a known inhibitor of adrenal steroid synthesis. While Janssen focuses on differences between ketoconazole and abiraterone (PBr. 51-52; PFOF 868-885), both were known to inhibit CYP17, lower cortisol, and skew the balance of the ACTH feedback loop (DFOF 386-389).

In 2006, ketoconazole unquestionably would have informed the POSA's predictions on abiraterone because the prior art frequently analogized the two (*see*, *e.g.*, DTX 1129.2, 7; DTX 1062.1; JTX 8037.3; DTX 1157.7). The PTAB found ketoconazole would have informed a POSA (DFOF 382-385), and this Court should too.[12] Contrary to the prior art, Janssen argues that

[12] While Janssen proposes that Gerber did not teach that ketoconazole and prednisone led to

abiraterone is different because corticosterone could compensate for any reduced cortisol caused by abiraterone, and presents this option as a certainty. PBr. at 47; PFOF 905, 916, 932. In truth, the prior art in 2006 never confirmed whether corticosterone—a mineralocorticoid with some glucocorticoid activity in humans—could even be *produced* in the high quantity necessary to have a chance at compensating for patients' low cortisol. DBr. 40-42, 45-46; JTX 8072.3 ("However, because corticosterone is a weaker glucocorticoid than cortisol [in humans, as opposed to rodents], abnormally high corticosterone production is necessary before feedback inhibition of pituitary ACTH secretion occurs"). Moreover, Attard 2005 recognized that *if* enough corticosterone could be produced, the POSA would expect elevated mineralocorticoid levels. JTX 8072.3 ("To produce enough corticosterone to compensate for the absence of cortisol, more intermediate steroids might be generated. . . . This ACTH-driven overproduction of mineralocorticoids often leads to hypertension," a side effect of mineralocorticoid excess).

Similarly, it is a mistake to say that a POSA would not have expected adrenal insufficiency, because that "requires deficiency in *both* cortisol and corticosterone." PBr. at 47; PFOF 895-896, 902, 904-905, 907, 915. No literature says that, and it contradicts the leading Harrison's textbook. DTX 1096.30 (instructing that adrenal insufficiency should be diagnosed by measuring cortisol through Synacthen test administration, not any other glucocorticoid or corticosterone). The PTAB rejected Janssen's unscientific argument that a POSA would have needed other glucocorticoids' levels before being able to predict whether abiraterone may cause adrenal insufficiency. DFOF 371. As recognized by the PTAB, the prior art reported that abiraterone blocked cortisol, and thus

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clinical improvement, that is not supported by any trial testimony; and the second page of the exhibit cited for support contains the Gerber authors' explanation supporting clinical benefit of the combination. PFOF 873; JTX 8033.3-4. Also, it is not credible to say that ketoconazole could be safely administered without a glucocorticoid (PBr. 52; PFOF 884-885), as that ignores the trial testimony that this was only possible in very low doses (DBr. 39).

a POSA would have predicted adrenal insufficiency. DFOF 364. We address Janssen's other complaints of the O'Donnell Synacthen test (PFOF 906-917) in our opening brief. DBr. 42-46.

In essence, Janssen insists that a POSA, in daily clinical practice and charged with doing no harm to his or her patient, would have waited for "insidious" side effects to occur before taking corrective action. PBr. 47-50; PFOF 886-950; JTX 8060.1 (calling adrenal insufficiency symptoms "insidious and thus difficult to recognize"); DTX 1096.29 (same). Janssen claims that Dr. Bantle "acknowledged that because the condition often progresses slowly, physicians could diagnose and treat it long before it caused harm, obviating the need to provide prednisone prophylactically." PBr. 53 n.28; PFOF 897. Actually, Dr. Bantle recommends the *exact opposite*, explaining that it was dangerous to sit and wait because symptoms were insidious and difficult to detect. DBr. 43-44.

To arrive at its remarkable position, Janssen advocates ignoring express warnings in the prior art. PBr. 48. Clinical trials require monitoring patients frequently, informing them of risks and obtaining their consent, and taking extensive steps to address any remotely expected adverse event. For example, abiraterone-only studies (PBr. 50; PFOF 949-950) incorporated heavy protections for handling abiraterone's "expected" (in Cougar's words) adrenal side effects, including the option to co-administer a glucocorticoid such as prednisone. DBr. 44-45. Doctors who see prostate cancer patients more infrequently would not shoulder these risks. DBr. 43-45. Janssen advocates a dangerous approach to medical treatment that runs counter to a POSA physician's oath to "do no harm." *Cf.* Tr. 1148:16-25 (Mega). By relying on post-priority studies conducted without a glucocorticoid, Janssen is engaged in hindsight. In fact, a patient enrolled in a study experienced the very same side effect our experts mentioned, and that patient died. Soon after, Cougar mandated using prednisone in every single one of its abiraterone studies. DBr. 44.

Even assuming O'Donnell did not conclusively mandate concomitant prednisone (*see*, *e.g.*,

PFOF 887-894, 911, 917),[13] O'Donnell still motivated a POSA to find out whether it was necessary to administer prednisone. DBr. at 37-39. In 2006, the prior art regarding adrenal steroid synthesis inhibitors such as abiraterone would have motivated a POSA to administer prednisone to mitigate abiraterone's side effects, and a POSA would reasonably have expected success based on past use of glucocorticoids. DBr. at 37-46. It was not inventive for Janssen later to determine exactly why concomitant prednisone was, in fact, necessary.

c. A POSA would have been motivated to use prednisone for its palliative effects

As it must, Janssen acknowledges that prednisone was given with prior art chemotherapies partly to palliate chemotherapy-related side effects, but insists that a POSA would not have been motivated to use prednisone for palliation with abiraterone because that is not chemotherapy. PBr. at 55. But in 2006, prednisone was known to palliate symptoms of advanced prostate cancer, in addition to palliating chemotherapy-related side effects. DBr. at 50-52. As of 2006, abiraterone was suggested as a second-line treatment for advanced prostate cancer (DTX 1129.1, 8; DTX 1157.8), an advanced disease that came with painful symptoms that prednisone was well known to palliate. DBr. at 50-52.

Janssen doubles down on its trial arguments that a POSA would not have been motivated to co-administer prednisone for palliation of abiraterone patients, because simply treating the patients' cancer is better than treating the cancer and simultaneously providing palliation to help the patient feel better. PFOF 954-958. Again, this argument ignores that many abiraterone patients have advanced, metastatic disease, which often carries the burden of painful symptoms. DBr. at 50-52.

[13] Janssen tries similarly to walk away from Attard 2005's clear disclosure. *See*, *e.g.*, PFOF 933. While Janssen wishes for the '438 patent to only be obvious when each patient's manifested side effects are determined with 100% certainty, that is not the legal standard. *See* Section II.B, *supra*.

A POSA would have expected prednisone to assuage these symptoms while abiraterone was working to treat the disease itself. *Id*.

To avoid this conclusion, Janssen claims that Dr. Lipton "conceded at trial that palliation did not provide an independent motivation to combine the two drugs." PBr. at 54-55; PFOF 960, 964. But Dr. Lipton testified that an independent reason to give prednisone to prostate cancer patients was palliation—because "they have decreased appetite, they have fatigue, they have difficulties with activities of daily life, and prednisone increases their sense of well-being, will help decrease a lot of those side effects. Pain, also." Tr. 1744:12-18 (Lipton); DFOF 424, 429; DTX 1076.3 ("[C]orticosteroids…provide palliation to some patients when used alone."); Tr. 1745:1-8 (Lipton) ("So, what we're saying is that prednisone has palliative benefits and that's another benefit of combining abiraterone with prednisone and treating cancer patients for the palliative benefit."); *see also* Tr. 1747:5-9 (Lipton). Here, too, Janssen is mistaken.

3. A POSA would have reasonably expected success in combining abiraterone and prednisone in therapeutically effective amounts.

Stepping back, Janssen is urging the Court to apply a double standard. On the one hand, Janssen argues that Defendants infringe the '438 patent if their labels call for administering 1000 mg abiraterone and 10 mg prednisone/day, because that is all the claims require. PBr. 9, 23-24. But in opposing obviousness, Janssen asserts that the claims would be obvious only if a POSA would have combined abiraterone and prednisone with a reasonable expectation of success in achieving "clinical efficacy"—including a survival benefit. PBr. 56-57 (including citation back to PBr. at 37-41); PFOF 984-993. As discussed, the proper test is guided by the actual claim elements, which require that both abiraterone and prednisone fight cancer, but do not require achieving improved survival.

Indeed, the claims would have been obvious if a POSA would have been motivated to

combine abiraterone and prednisone in what Janssen argues are therapeutically effective amounts with a reasonable expectation of success. It is counterfactual to say that the prior art suggested that neither abiraterone nor prednisone would successfully treat prostate cancer. PBr. 57. The evidence showed that it would have been obvious to combine abiraterone with prednisone, and that a POSA would have done so in the claimed amounts. DFOF 432-438, 488; *see also supra* Sec. II.B.2. Further, the language of the claims does not require either a synergistic anti-cancer effect or a particular efficacy threshold other than that required by the Court's claim construction (e.g., "management or control of … metastatic cancer cells or tissue and the minimization or delay of the spread of cancer"). ECF No. 239 at 30. Therefore, the evidence clearly and convincingly established a reasonable expectation of success in administering the claimed amounts of prednisone and abiraterone.

Obviousness requires a reasonable expectation of success, not certainty. DBr. at 34-35. A POSA in 2006 did not need a guarantee that prednisone would fight cancer or a proven survival benefit. A POSA only needed to perceive a reasonable expectation of success in achieving the claimed invention. *Alza Corp. v. Mylan Labs. Inc.* 464 F.3d 1286, 1295 (Fed. Cir. 2006); *Pfizer*, 480 F.3d at 1364. Here, the human clinical results presented in the prior art for abiraterone (*e.g.* in O'Donnell) and prednisone (*e.g.* in Sartor) would have given the POSA that reasonable expectation. *See*, *e.g.*, DFOF 441.

C. Janssen's Secondary Considerations Cannot Overcome the Strong Showing of Obviousness.

While Defendants always retain the ultimate burden of proving obviousness, Janssen "bore the burden of producing evidence of objective indicia" of non-obviousness. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, Nos. 2017-2078, 2017-2134, 2018 WL 4288982, at *20 (Fed. Cir. Sept. 10, 2018). None of Janssen's purported objective indicia "overcome the strong showing of

obviousness" here. *Pfizer*, 480 F.3d at 1372.

1. Janssen failed to prove a nexus to the '438 patent's purportedly novel feature.

It is a "fundamental requirement" that the proponent of any secondary considerations of non-obviousness establish a nexus to the claimed invention. *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). Where, as here, commercial success, unexpected results, industry praise, or other considerations arise from an element in the prior art or "something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention." *Id*. (emphasis added) (collecting cases). Janssen argues that "Defendants failed to show that the success of Zytiga is due to extraneous factors unrelated to the '438 patent." PBr. at 59. But Janssen must prove the required nexus, not Defendants, *Kao*, 639 F.3d at 1068, and it failed to do so here.

The prior art disclosed abiraterone and its use to treat prostate cancer. DFOF 295-297. The allegedly novel feature of the '438 patent is using abiraterone *with prednisone* to treat prostate cancer (the '213 patent already claimed abiraterone for this use). And the Court construed the patent claims to require that both abiraterone and prednisone fight cancer. Although Janssen urges that Mr. Hofmann somehow admitted a nexus (PFOF 1018), he was explaining why there is *none*—because while prednisone may be co-administered with abiraterone, the marketplace success was due to prior art factors. Tr. 2062:1-2064:2 (Hofmann).

Grasping at straws still further, Janssen observes that clinicians frequently prescribe abiraterone and prednisone together for prostate cancer and argues that "all three oncologists who testified at trial affirmed that they prescribe abiraterone with prednisone." PBr. at 59; PFOF 1005-1011. But no number of prescriptions for that combination suffices to show nexus to the allegedly novel aspect of the '438 patent claims. Clinicians prescribe prednisone in the combination for reasons other than treating cancer. For example, two of the three oncologists testified that they

prescribe prednisone to ameliorate abiraterone's side effects and for prednisone's palliative effects, *not* for any anti-cancer benefit. Tr. 1148:16-1149:3 (Mega); Tr. 1644:18-1645:4 (Lipton). Janssen itself touts these non-cancer benefits in its Zytiga promotional materials. DFOF 571. And Janssen's commercial success expert, Dr. Vellturo, admitted that he made no effort to determine how much of Zytiga's demand arises from abiraterone's anti-cancer effects, or prednisone's non-cancer effects, compared to prednisone's alleged anti-cancer effects. DFOF 573-575. But that is absolutely crucial. Janssen failed to prove the required nexus between its objective indicia and the '438 patent claims.

2. Janssen's evidence of commercial success, long-felt unmet need, and failure of others is undermined by the '213 blocking patent.

Janssen's evidence of commercial success, long-felt but unmet need, and failure of others also run headlong into the prior art '213 blocking patent, which claimed abiraterone and its use to treat prostate cancer. "A patent has been called a 'blocking patent' where practice of a later invention would infringe the earlier patent." *Acorda*, 2018 WL 4288982 at *18 (applying the blocking patent analysis to commercial success, long-felt need, and failure of others). "The existence of such a blocking patent may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, 'blocked' invention, because of the risk of infringement liability and associated monetary or injunctive remedies." *Id*. The "potential deterrent effect is relevant to … evaluating objective indicia of the obviousness of the later patent," including commercial success, long-felt need, and failure of others. *Id*. at *18, *22. An exclusively licensed patent "suggest[s] the significance of the . . . patent's blocking power." *Id*. at *21. That is especially true where "[any] improvements will be entirely covered by the blocking patent." *Id.* at *19. Indeed, the Federal Circuit recently affirmed a finding that gave little weight to evidence of commercial success, long-felt need, and failure of others, in view of a blocking patent. *See id*.

at *19-21.

Here, Janssen cannot dispute that the '213 patent was the subject of an exclusive worldwide license to Cougar Biotechnology as of April 2004. DFOF 584. And ***any*** use of abiraterone would be blocked entirely by the '213 patent. That powerfully deterred anyone other than Cougar—abiraterone's exclusive licensee—from commercializing the '438 patent's later-claimed treatment of prostate cancer using abiraterone and prednisone.

To avoid this conclusion, Janssen criticizes Defendants' expert Mr. Hofmann as being "myopically focused on the period after Cougar's exclusive license, with no reasonable justification." PBr. at 61. The opposite is true. The key O'Donnell reference, as well as Attard 2005 and Garnick 2006, became publicly available only *after* Cougar secured its exclusive license. DFOF 585-587. The real question is why Janssen's commercial success expert Dr. Vellturo virtually ignored this critical period, when the art disclosing abiraterone's promise for treating prostate cancer was being published and gaining momentum. As to that period, Dr. Vellturo speculated only that a POSA might have somehow persuaded Cougar to sublicense its exclusive rights to the '213 patent, or that someone could have bought Cougar outright. This argument ignores the unique power of an *exclusive* patent license, and, if accepted, could always trump the real-world impact of a blocking patent. At a minimum, Janssen needed to present *evidence* that during the crucial period between the issuance of Cougar's exclusive license to the '213 patent and the '438 patent's priority date, Cougar was willing to sublicense the '213 patent on reasonable terms, or to be acquired. After all, Courts consider "the risk that the blocking-patent owner (making its own economic calculations, perhaps in light of its own other products or research activities) will altogether refuse to grant a license to the improvement or will demand so large a share of profits that the whole project is not worthwhile for the potential innovator … in light of other investment

opportunities." *Acorda*, 2018 WL 4288982 at *19. But here, Janssen presented *no evidence* that Cougar was willing to sublicense the '213 patent on *any* terms after acquiring its exclusive rights, much less that Cougar was shopping itself as a takeover target. DFOF 588-589.

Janssen also argues that "[f]ar from being blocked by the '213 patent, the pharmaceutical industry received BTG's sales pitch for abiraterone and declined." PBr. 61; PFOF 1028-1049. That argument is flawed for two reasons. First, as discussed, it ignores the critical period between the April 2004 exclusive license to Cougar and the '438 patent's August 2006 priority date—a period when key prior art first became public. Second, it is a gross overstatement of BTG's licensing activity between 1999 and 2004. Janssen's only licensing fact witness (Dr. Judson) admitted he was not directly involved in BTG's licensing efforts beyond meeting with three companies on a single trip to the United States, in which he presented data on multiple different drugs, and had no idea why those companies did not license the '213 patent. Tr. 229:10-230:11; 233:10-18; DFOF 579-583. Janssen proposes that BTG was "continuously attempting to find a development partner for abiraterone acetate" before 2004. PFOF 1045. But the only evidence it cites is a snippet of Dr. Judson's testimony ("that's my understanding") (Tr. at 231:19-21 (Judson)), who admittedly was not directly involved in licensing. Janssen identified no licensing correspondence or other documents to support Dr. Judson's cursory testimony. Janssen's speculation as to why Boehringer failed to develop the '438 invention suffers from the same lack of support. PFOF 1071-1074.

3. Janssen failed to produce meaningful evidence of long-felt need, failure of others, skepticism, or industry praise.

Janssen's objective indicia evidence was also thin. According to Janssen, different prostate cancer drugs tested by others through the years failed to show a survival benefit (again improperly assuming that all such drugs are "ineffective"), and created a long-felt need for better treatments. That ignores the state of the art concerning abiraterone *at the priority date*, including O'Donnell

and later publications. Failed efforts that "preceded publications that would render the invention obvious to those of skill in the art" are "not particularly probative." *Acorda*, 2018 WL 4288982 at *22. And "[i]n receiving evidence of unsuccessful research, courts must take care that such research was conducted under the same state of the art as that which confronted the patentee." *Id*. (citation omitted). Janssen made no effort to do that here.

The same flaw afflicts Janssen's industry-skepticism argument (PBr. 62-63), which relies on a 1999 article questioning research into hormonal manipulations and BTG's purported licensing struggles before 2004. And it does not show industry-wide skepticism about abiraterone to observe that one out of two reviewers[14] of the O'Donnell article expressed some skepticism about "the role of androgens in stimulating prostate cancer growth in castrate men"—especially when the other reviewer expressed the opposite sentiment about abiraterone. DBr. at 63; JTX8064.2-3; DFOF 598-600, 602-603; Tr. 1623:8-19 (Lipton). Most importantly, it does not amount to any skepticism of the claimed invention of administering abiraterone with prednisone.

Janssen also argues industry praise, but to no avail. It says a paper described the COU-AA-301 study as "stunning" and "dramatically alter[ing] our view of hormonal treatment in advanced-stage prostate cancer." PBr. at 65 (citations omitted). In fact, what the article described as "stunning" was the sheer number of promising "therapies that target metastatic prostate cancer recurring after initial androgen deprivation," identifying abiraterone (not abiraterone plus prednisone) as "the fourth" of five agents "shown to prolong overall survival." PTX 50 at 515. And here again, even this reaction was limited to abiraterone alone—not its combination with prednisone.

[14] Janssen incorrectly suggests that multiple reviewers (instead of just one) included comments that could be construed as skepticism of further androgen deprivation. PFOF 1062-63.

4. Janssen has not established unexpected results.

The '438 patent claims the use of abiraterone and prednisone to fight cancer. As discussed in Section I.A., Janssen has not established that prednisone actually fights cancer when administered with abiraterone—and the evidence certainly does not establish that prednisone doubles abiraterone's effect.[15] Even apart from direct infringement, Janssen's tenuous evidence of prednisone's anti-cancer effects—which is challenged by Defendants on all fronts—is not sufficient to support unexpected results. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) (affirming district court's obviousness determination of no unexpected results because the plaintiff's clinical study results were "inconsistent, not shown to be reproducible, and did not include comparative data … necessary to demonstrate unexpected or synergistic effects.").

Moreover, as explained in our opening brief, even if Janssen had shown that prednisone contributed some anti-cancer effect to the combination, it would represent a difference in degree, not in kind. DBr. at 62. The PTAB has agreed, on the same evidence, that there are no unexpected results. DFOF 503.

D. The '438 patent lacks a sufficient written description of the claimed invention.

Janssen posits that a POSA before August 2006 would not have expected prednisone to treat cancer effectively, and even further, that a POSA would not have expected *abiraterone* to be effective. PBr. at 37-46. And Janssen's entire obviousness rebuttal revolves around a theme of confusion and unpredictability in the art. *Id*. Yet Janssen asserts that the moment the claims were written in the '438 patent, only a few of which call 1000 mg/day abiraterone and 10 mg/day prednisone "therapeutically effective" (while others deem ranges as low as 0.01 mg/day prednisone

[15] Janssen argues that Defendants' expert Dr. Mega "agreed that the results of the extension study were unexpected" (PBr. 65; PFOF 1055), but Dr. Mega was only responding to an unrelated hypothetical question. Tr. 1264:12-17.

to be therapeutically effective), a POSA would automatically have understood that both agents effectively treat prostate cancer. DBr. 69-70. But neither Janssen nor the public had any extension study data until after 2007, when the extension study enrolled its first patient. Tr. 2028:13-16 (Rettig). But "research hypotheses do not qualify for patent protection." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1353 (Fed. Cir. 2010).

Of course, "the hallmark of written description is disclosure," and "[t]he specification must describe an invention understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed." *Id.* at 1351. As our trial evidence showed, the '438 patent does not describe an invention in which both abiraterone and prednisone fight prostate cancer, and it certainly does not describe the alleged synergistic effect that makes the alleged claimed invention possible.[16]

Janssen presents a few quotes from the '438 patent specification, claiming they teach the POSA that the prednisone doses claimed in the '438 patent fight cancer when administered with abiraterone. PBr. 68-69; PFOF 1092-1094. But one quote Janssen highlights teaches that prednisone is *not* an anti-cancer agent. JTX 8000.7 ("an anti-cancer agent *or* steroid, particularly a glucocorticoid") (emphasis added). The other quotes suffer from the same defect seen throughout Janssen's infringement case: The specification does not teach to a POSA that prednisone helps abiraterone fight cancer. And although the '438 patent is directed to methods of treating prostate cancer, prednisone is listed as one possible agent in a list of 352 possibilities. DBr. 68.

These passing mentions to prednisone in the specification do not rise to the level of adequate written description, because they do not teach a POSA that prednisone—not to mention other agents

[16] In fact, neither synergy, reversal of resistance, nor Dr. de Bono's theory was mentioned in the patent specification during the entire prosecution of the '438 patent. *See generally* JTX 8001.

such as Vitamin A, Vitamin D, and ibuprofen—actually fights cancer. DBr. 68; *see Wyeth v. Abbott Labs.*, No. 08–230, 08–1021, 2012 WL 175023, at *6-*10 (D.N.J. Jan. 19, 2012) (finding claims to various drug administrations, including rectal and transdermal administration, lacking written description despite limited descriptions that the drug may be administered rectally or transdermally, when the patentee had never attempted these forms of administration). Although there is no "rigid requirement" that the specification contain examples or an actual reduction to practice (PBr. 68), Janssen cannot have it both ways. If indeed a POSA lacked understanding of abiraterone's and prednisone's efficacy at the priority date, nothing in the specification of the '438 patent would convince the POSA that these agents actually fight cancer. DBr. at 67-70; *Ariad*, 598 F.3d at 1351 ("[T]he level of detail required to satisfy the written description requirement varies depending on . . . the complexity and predictability of the relevant technology.").

In a last-ditch effort to remedy the specification's lack of disclosure, Janssen claims that its specification does not actually need to tell the POSA anything about prednisone's anti-cancer effects, asserting that "the anti-cancer effect of prednisone is an inherent property of formulations described in the specification." PBr. at 69. Janssen's own data proves this argument wrong. Even putting aside all flaws in the studies Janssen presented at trial, the dexamethasone extension study only showed a small portion of patients exhibiting a PSA response possibly related to dexamethasone, and an even lower proportion of patients responded when Janssen eventually decided to start replicating this study design with prednisone. DBr. 11-13; DTX 1712.2 (reporting only 8.3% of patients having any PSA decline at all, and only 1 patient receiving a ≥50% decline). Janssen's data shows that if prednisone has an anti-cancer effect (it does not), it is only in a small proportion of patients; it is not inherent.

E. Estoppel does not bar Defendants' obviousness defense.

Janssen continues to insist that Defendants are estopped from defending against Janssen's

claims because we have *succeeded*, three separate times, in having every claim of the '438 patent held unpatentable by the PTAB, the PTO's expert board of scientifically trained patent-law judges.[17] Janssen openly admits that it is trying to use the IPR decisions to secure injunctive relief premised on a patent already held invalid by the very agency that issued it. Tr. 23:22-25:21. Under Janssen's theory, Defendants are actually worse off for having prevailed in the PTO. That is exactly the type of absurd result that principles of statutory construction safeguard against. *See United States v. Ron Pair Enters.*, 489 U.S. 235, 242 (1989) ("The plain meaning of legislation should be conclusive, except in the 'rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters.'" (alteration in original) (quoting *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 571 (1982)); *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661, 678-79 (1990) (construing 35 U.S.C. § 271(e)(1) to avoid an interpretation of the statue that would require "an implausible substantive intent"). The very concern that gave rise to the American Invents Acts was, as stated by Congressman Goodlatte, one of the chief sponsors of the AIA, "*invalid patents … be[ing] used by aggressive trial lawyers to game the system.*" ECF No. 418-6 at H4426 (emphasis added). That is exactly what Janssen is trying to do here. The AIA was intended to curb abusive assertions of invalid patents, not to punish successful petitioners.

Janssen's argument also fails as a matter of administrative law. Having lost three different IPRs, Janssen's last hope was to seek rehearing. Janssen's brief wholly failed to address the impact of its rehearing requests on the application of section 315(e)(2)'s estoppel provision. Janssen's decision to seek rehearing rendered the IPR decisions non-final, meaning the estoppel statute does not apply here under *any* interpretation. Whatever its scope, section 315(e)(2) applies only where

[17] The Court denied Janssen's *motion in limine* at trial (Tr. 25:24-28:12; ECF No. 520), and the Court should do the same here.

there is a *final* written decision. A decision is "final" under the PTO's regulations, and bedrock principles of administrative law, only when the decision is available for judicial review. 37 C.F.R. § 42.2. ("Final means final for the purpose of judicial review to the extent available. A decision is final only if it disposes of all necessary issues with regard to the party seeking judicial review, and does not indicate that further action is required."); *West Penn Power Co. v. EPA*, 860 F.2d 581, 583 (3d Cir. 1988) ("the pendency of the reconsideration petition deprives the agency decision of finality"); *Utility Air Regulatory Grp. v. EPA*, 744 F.3d 741, 746 (D.C. Cir. 2014) ("This court's general view is that a pending petition for agency rehearing renders the underlying agency action nonfinal (and hence unreviewable) with respect to the filing party." (alterations omitted) (internal quotations omitted) (citations omitted)). Here, Janssen's motion invites the PTAB to take further action, and "reset[s] the time for appeal or civil action to no later than sixty-three (63) days after action on the request" (37 C.F.R. § 90.3(b)(1))—thus preventing judicial review of the decisions. In light of Janssen's actions, the estoppel statute does not apply here.

III. The Court should exclude Janssen's expert testimony from fact witness Dr. de Bono and reject Janssen's request to exclude testimony from Drs. McKeague and Mega.

Finally, Janssen objected to certain testimony from Drs. Mega and McKeague at trial, but those objections correctly were not sustained. In contrast to Janssen's fact witness Dr. de Bono, the general subject matter of Drs. Mega and McKeague's testimony (e.g., the Attard 2008 and 2009 articles) was disclosed in their respective expert reports; both reviewed the underlying publications and included them on their materials considered lists; and both were responding to undisclosed opinion testimony by Janssen's fact and expert witnesses. *Compare* Tr. 165:2-166:11 (de Bono), Tr. 722:7-723:8, 2022:12-18 (Rettig), *with* Tr. 936:12-937:15 (McKeague), Tr. 1183:3-1191:20 (Mega); *see also* Tr. 1184:12-13 (Mega).[18]

[18] Janssen's request seeks only to strike testimony where Drs. Mega and McKeague addressed

Defendants reiterate their request to exclude all undisclosed expert testimony from Janssen's fact witness and inventor Dr. de Bono. Janssen's opening brief and proposed facts reveal that Janssen is trying to shore up its case by smuggling in undisclosed expert testimony from its fact witness inventor. That is not allowed—not only because it is too late, but because fact witnesses cannot provide expert testimony. *See*, *e.g.*, Fed. R. Evid. 701. That is especially true where the witness is a self-interested inventor attempting to save his own patent. Janssen uses Dr. de Bono's testimony to support a litany of expert assertions, permeating most of its non-obviousness case.[19] In fact, many expert assertions throughout Janssen's brief and proposed facts are *solely* supported by the testimony of Dr. de Bono.[20] None should be given any weight.

Finally, many of Janssen's proposed fact findings also rely on hearsay to support purported licensing difficulties and skepticism of abiraterone.[21] Janssen should not be able to rely on the testimony of a fact witness not involved in the licensing process to support licensing difficulties, or an inventor's testimony about what colleagues told him about abiraterone's prospects to support skepticism of the drug. This testimony should similarly be disregarded.

CONCLUSION

For all these reasons, the Court should find that (1) Defendants do not infringe any of the asserted claims of the '438 patent and (2) each of the asserted claims is also invalid as obvious or,

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certain aspects of the 001 study and Dr. Rettig's cross study comparison. *See* PBr. at 15 (requesting to strike Tr. 936:12-937:21, 943:3-947:3, 1183:3-1184:2, 1184:7-1191:20). In its findings of fact, Janssen attempts to undermine other testimony by Drs. Mega and McKeague as "undisclosed." These arguments are waived because they do not appear in Janssen's brief.

[19] PBr. 2-5, 11, 37-38, 44-46, 56-57, 62-64; PFOF 41, 46, 57-58, 723-725, 737-738, 745-746, 768, 778, 809, 833, 845-849, 852-853, 855-857, 970-971, 973, 975, 982, 984-989, 991-992, 1057, 1074-1077, 1079, 1086.

[20] PBr. 3, 11, 37-38, 44-45; PFOF 95, 123-124, 138, 196, 359, 723, 737, 778, 845-847, 849, 852, 857, 950, 982, 986, 1074.

[21] *See*, *e.g.*, PFOF 96-97, 777-778, 780-782, 790, 1037, 1045, 1061, 1064, 1071, 1073-1074.

in the alternative, for lack of adequate written description. Alternatively, in view of the PTAB's decisions, Defendants reserve the right to challenge any ruling that would delay a generic launch.

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CERTIFICATION OF SERVICE

I hereby certify that on September 21, 2018 copies of the foregoing Defendants' Post-Trial Response Brief and supporting documents were electronically filed and served by notice of electronic filing upon all counsel of record.

I certify that the foregoing statements made by me are true. I am aware that if any of the foregoing statements are willfully false, I am subject to punishment.

s/ James S. Richter
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Dated: September 21, 2018